

**REMARKS**

**I. Summary of the Office Action and this Reply**

Claims 1-46 are pending; claims 19-28 have been withdrawn from consideration. The Examiner has rejected claims 1, 5-12, 15-18, 29-30, 32-34, 36 and 45 under 35 U.S.C. §102(e), asserting that such claims are anticipated by U.S. Patent No. 6,673,620 to Loeffler et al. ("Loeffler"). The Examiner has rejected claims 1-10, 16-18, 29-36 and 45 under 35 U.S.C. §102(b), asserting that such claims are anticipated by U.S. Patent No. 5,192,503 to McGrath et al. ("McGrath"). Further, the Examiner has rejected claims 1-7, 17-18, 29-31 and 45, asserting that such claims are anticipated by U.S. Patent No. 4,738,824 to Takeuchi ("Takeuchi"). Further still, the Examiner has rejected claims 11-15 and 37-46 under 35 U.S.C. §103(a), asserting that such claims are obvious over McGrath. Finally, the Examiner has rejected claim 1 under 35 U.S.C. §112.

In this Reply, claims 1, 3-7, 12, 13, 17, 29, 31, 37, 45 and 46 are amended; claims 19-28 are canceled; new claims 47-55 are added. No new matter is added; support for the amendments can be found, inter alia, at page 8, lines 26-32, page 16, lines 1-14, page 20, line 30 – page 21, line 7, and page 27, lines 4-24.

**II. Response to 102 Rejections**

A rejection under 35 U.S.C. §102 is proper only if each and every element of the

claim is found in a single prior art reference. MPEP § 2131. The Examiner has rejected claims 1-10, 16-18, 29-36, 45 and 46 under 35 U.S.C. §102, asserting that each and every element of these claims are found in Loeffler, McGrath and/or Takeuchi.

**Claims 1, 17, 18, 47, 54 and 55**

Independent claim 1 is directed to a device for conducting processing steps on a substrate comprising an array of chemical compounds on a surface thereof, and stands rejected over Loeffler, McGrath and Takeuchi.

Claim 1 recites that the device includes "a housing comprising a housing chamber" and "an opening in said housing adapted for insertion into said housing chamber of a substrate having a surface comprising an array of chemical compounds." The Examiner asserts on page 4 of the Action that claim 1 is anticipated by Loeffler, stating "Loeffler et al. disclose a sample chamber is formed by a housing sealed against a microscope slide . . . . The reagent may be sealed within a confined cavity, or 'chamber', so as to prevent evaporation . . . . One surface of this chamber is the flat side surface. The remaining surfaces are formed by a cell. The cell is preferably a plastic disposable part that fits on top of the slide . . . . The cell forms a fluid seal to the surface of the glass by means of a gasket." Accordingly, the Examiner asserts that Loeffler's microscope slide 9, which bears a biologic sample, and gasket 3 make up the claimed housing chamber. See col. 6, lines 3-7. However, this is clearly contrary to the language of claim 1, which requires a substrate having a surface comprising an array of

chemical compounds, a housing having a housing chamber, and an opening adapted for insertion of the substrate into the housing chamber. In Loeffler, there is no housing having an opening adapted for insertion of a substrate into the housing's housing chamber, as recited by claim 1. For at least this reason, Loeffler fails to disclose each and every element of claim 1, and reconsideration and withdrawal of the rejection of claim 1 over Loeffler are requested respectfully.

With respect to McGrath, the Examiner appears to assert on pages 6 and 7 of the Action that claim 1 is anticipated by the wash means and case 73 described with respect to Figures 3 and 9. The case 73 has receptacles 140 into which slides 50 containing individual tissue sections or cell groups 52 are inserted. Col. 12, lines 35-37. Reagent on a tissue section of each slide 50 is moved from a reaction chamber 56 formed between each slide 50 and its corresponding problem clip 10 into a mixing chamber 58. This moving is achieved by simply rotating the case 73 from a horizontal to a substantially vertical position and allowing the reactant fluid to move through one or both of the fluid communication channels 26, 28 formed on the probe clip. Col. 12, lines 55-63.

After completion of incubation, the probe clips 10 may be washed by injection of fluid into the inlets 178 of each receptacle in the case 73. This washing removes all traces of the probe and reactant from the tissue sections 52. The wash fluid is evacuated or drained through the outlet ports 180. Col. 13, lines 10-23. All of the wash fluid within each receptacle may be removed by tilting or disposing the case 73 vertically

with the front wall 130 being positioned in a downward facing direction or by applying a vacuum or suction force to the outlet 180 to draw all the fluid from the receptacle. This washes each slide so as to remove all traces of unreacted probe and reagent from the tissue mounted on the slide without contaminating adjacent samples. Col. 12, lines 1-10.

Accordingly, McGrath teaches that mixing of the reagent and tissue samples rotating the case 73 from a horizontal to a substantially vertical position and allowing the reactant fluid to move through one or both of the fluid communication channels 26, 28 formed on the probe clip. Col. 12, lines 55-63. McGrath further teaches that a slide may be washed by adding wash fluid to receptacles, and then removing the wash fluid, etc. by essentially dumping the receptacle, i.e. by "tilting or disposing the case 73 vertically with the front wall 130 being positioned in a downward facing direction or by applying a vacuum or suction force to the outlet 180 to draw all the fluid from the receptacle. This washes each slide . . ." Col. 12, lines 1-10.

However, there is no teaching or suggestion in McGrath of a fluid separation mechanism that separates fluid from a substrate "in a controlled manner that preserves the integrity of the fluid meniscus at the atmosphere-fluid interface", as required by claim 1. As described in the application, separation of fluid from the substrate in a controlled manner provides a substantially dry substrate surface in that it substantially eliminates fluid droplet formation on the substrate, because the existing surface tension of the fluid in conjunction with the level of hydrophobicity or hydrophilicity of the

substrate surface discourages or avoids the formation of isolated droplets separate from the major fluid mass. See page 16, lines 1-19. Accordingly, McGrath fails to disclose each and every element of claim 1, and reconsideration and withdrawal of the rejection of claim 1 over McGrath are requested respectfully.

With respect to Takeuchi, Takeuchi discloses an automatic dyeing apparatus for dyeing specimens. The apparatus includes a transport mechanism T for transporting specimen cages into vessels v holding water or reagent. However, Takeuchi has no disclosure whatsoever of a fluid separation mechanism that is configured to separate fluid from a substrate "in a controlled manner that preserves the integrity of the fluid meniscus at the atmosphere-fluid interface", as required by claim 1. Accordingly, Takeuchi fails to disclose each and every element of claim 1, and reconsideration and withdrawal of the rejection of claim 1 over Takeuchi are requested respectfully.

Claims 17 and 18 depend from claim 1 and are likewise patentable. In addition, claim 17 positively recites that the device further comprises the substrate positioned within the housing chamber which addresses the Examiner's comments in paragraphs 3 and 5 of the Action with respect to claiming of the substrate.

New claim 47 is substantially similar to claim 1, but recites "a fluid separation means for separating fluid from contact with said substrate in a controlled manner so that the integrity of the fluid's meniscus at the atmosphere-fluid interface is preserved." Accordingly, claim 47 is believed to address the Examiner's comments in paragraph 3 of the Action.

New claim 54 recites that the controlled manner provides for a constant velocity of flow of fluid reagent during its removal from the housing chamber. New claim 55 recites that the controlled manner provides for a constant velocity of flow of fluid reagent during its removal from the housing chamber, as measured by a velocity of the fluid reagent's meniscus. See page 20, line 30 – page 21, line 7. This is neither taught nor suggested by the cited art.

For at least these reasons, reconsideration and withdrawal of the rejections of claims 1, 17 and 18, and allowance of new claims 47, 54 and 55, are requested respectfully.

**Claims 2-8, 10, 11, 14-16**

Claims 2-8, 10, 11 and 14-16 depend from claim 1 and are likewise patentable for the reasons set forth above for claim 1.

Additionally, claim 3 recites a lifting mechanism for lifting said substrate out of contact with said fluid in said controlled manner. Claim 4 further recites that the lifting mechanism lifts said substrate out of said housing chamber at a rate that substantially eliminates droplet formation of said fluid on said substrate. Such a rate, avoidance of such droplet formation by lifting at such a rate, and a lifting mechanism for doing so are neither taught nor suggested by the cited art.

Claim 5 further recites that the fluid separation mechanism is a fluid removal mechanism for removing fluid from said housing chamber in said controlled manner.

Claim 6 further recites that the fluid removal mechanism removes fluid from said housing chamber at a rate that substantially eliminates droplet formation of said fluid on said substrate. Such a rate, avoidance of such droplet formation by removing fluid at such a rate, and a fluid removal mechanism for doing so are neither taught nor suggested by the cited art.

For at least these additional reasons, the cited art fails to teach each and every claim element. Reconsideration and withdrawal of the rejections of claims 2-8, 10, 11 and 14-16 are requested respectfully.

**Claim 9**

Claim depends from claim 1 and is likewise patentable. In addition, claim 9 further recites that the fluid removal mechanism comprises a valve having a varying cross-section relative to height of fluid in said housing chamber. This is neither taught nor suggested by the cited art, and the Examiner has not asserted to the contrary. For this additional reason, the cited art fails to teach each and every claim element, and reconsideration and withdrawal of the rejection of claim 9 are requested respectfully.

**Claim 12**

Claim 12 depends from claim 1 and is likewise patentable. In addition, claim 12 recites a separator configured to separate a sandwich of a substrate and a cover slide inserted into said housing chamber. In paragraph 8 of the Action, the Examiner has

rejected claim 12 over Loeffler, but has not identified with specificity which portion of the reference is relied upon as the basis for the rejection. In any event, Loeffler does not disclose a housing chamber for receiving a substrate, as discussed above with reference to claim 1, and thus cannot disclose the claimed separator. For this additional reason, the cited art fails to teach each and every claim element, and reconsideration and withdrawal of the rejection of claim 9 are requested respectfully.

**Claims 29-36**

Claims 29-36 are directed to a method for performing a step of a hybridization reaction on the surface of a substrate. The method comprises inserting a substrate comprising an array of chemical compounds on a surface thereof into a housing chamber of a device according to claim 1. Accordingly, claims 29-36 are believed patentable for reasons similar to those set forth above for claim 1.

Further, claim 29 recites "introducing a fluid reagent . . . into said housing chamber" and "removing said fluid reagent from contact with said substrate in a controlled manner at a rate that substantially eliminates formation of droplets of said fluid on said surface of said substrate." There is no teaching or suggestion in the cited art of removing fluid from contact with a substrate "in a controlled manner at a rate that substantially eliminates formation of droplets of said surface of said substrate." As described in the application, removal of fluid from contact with the substrate in a controlled manner substantially eliminates fluid droplet formation on the substrate

because the existing surface tension of the fluid in conjunction with the level of hydrophobicity or hydrophilicity of the substrate surface discourages or avoids the formation of isolated droplets separate from the major fluid mass. See page 16, lines 1-19. For at least this additional reason, reconsideration and withdrawal of the rejection of claims 29-36 are requested respectfully.

Claim 31 further recites that the removing is carried out by lifting the substrate from the housing in the controlled manner. Claim 32 recites that the removing is carried out by a removal mechanism selected from the group consisting of (i) a valve having a varying cross-section relative to height of fluid in said housing chamber and (ii) a pump having a constant displacement. Accordingly, claims 31 and 32 are further patentable for reasons similar to those set forth above for claims 3, 4 and 9.

Claim 33 further recites "introducing a fluid vapor into said housing chamber during said removing to assist in drying said substrate surface." Claim 34 recites that the fluid vapor is a vapor of an organic solvent. As described in the application, the vapor creates a surface tension gradient at the atmosphere-fluid interface to preserve the integrity of the fluid meniscus, substantially eliminating droplet formation as the fluid recedes. Page 8, lines 18-25. The cited art does not teach introducing a fluid vapor into a housing chamber to assist in drying the substrate surface, as recited in claim 33.

For at least these additional reasons, reconsideration and withdrawal of the rejections of claims 29-36 are requested respectfully.

**Claims 37-44**

Claim 37 is directed to an apparatus for conducting a processing step of a hybridization reaction involving an array of biopolymers on the surface of a substrate. The apparatus comprises one or more devices according to claim 1. Accordingly, claims 37-44 are believed patentable for reasons similar to those set forth above for claim 1.

Additionally, claim 37 recites "a portion of a lifting mechanism external to said devices wherein said lifting mechanism lifts said substrate out of contact with a fluid reagent in a controlled manner that preserves the integrity of the fluid reagent's meniscus at the atmosphere-fluid interface." Accordingly, claim 37 is further believed patentable for reasons similar to those set forth above for claims 3 and 4.

For at least these reasons, reconsideration and withdrawal of the rejections of claims 37-44 are requested respectfully.

**Claim 45**

Independent claim 45 is directed to a flow device comprising a reaction chamber having an opening for insertion of a substrate into said reaction chamber. As discussed above with reference to claim 1, Loeffler does not disclose such a reaction chamber. Accordingly, reconsideration and withdrawal of the rejection of claim 45 over Loeffler are requested respectfully.

Further, claim 45 recites that the substrate has a cover slide over a surface

thereof, and that the flow device includes "a separator mechanism for separating said substrate surface and said cover slide while in said reaction chamber without damage to said biopolymers on said surface." As discussed above, the cited art does not disclose the recited separator mechanism for separating a substrate surface and cover slide while in the reaction chamber. Accordingly, reconsideration and withdrawal of the rejection of claim 45 over McGrath and Takeuchi are requested respectfully.

### **III. Response to 103 Rejections**

Claims 11-15 and 37-46 stand rejected under section 103 over McGrath.

A section 103 rejection is proper only if all claim limitations are taught or suggested by the cited art. MPEP §2143.

#### **Claims 11-15, 37-44, 48 and 51**

Claims 11-15, 37-44, 48 and 51 depend from claim 1, which is believed allowable for reasons set forth above, and are thus allowable.

Additionally, claim 12 recites a separator configured to separate a sandwich of a substrate and a cover slide inserted into said housing chamber. See Figure 8. The Examiner states on page 11 of the Action that "McGrath et al. further states it would also be desirable to provide an *in situ* assay apparatus in which the reaction chamber has sufficient vertical space between a cover slide and the tissue carrying slide to reduce friction for complete reactant mixing." See McGrath, col. 2, lines 9-13.

This vertical space in the reaction chamber is provided in McGrath probe 10, which includes seals and dividing means. At least one and preferably both of the first and second ends of the second seal member are spaced from adjacent portions of the first seal member to define fluid flow channels therebetween which form mixing and reaction surfaces in the interior cavity on the plate. Col. 2, lines 34-66.

As shown in FIGs. 1 and 6, the tissue section 52 is mounted on the slide 50 adjacent a first end 54 of the slide 50. When the slide 50 is joined to the probe clip 10, the tissue section 52 faces the reaction chamber surface 30 formed on the probe clip 10. The probe 40 is mounted on the mixing chamber surface 34 of the probe clip 10 and is spaced from the tissue section 52 by the second seal member 24. The joined probe clip 10 and slide 50, as shown in FIG. 6, form a reaction chamber 56 and a mixing chamber 58 therebetween. The reaction chamber 56 is formed about the tissue section 52 on the slide 50 and is surrounded by the second seal member 24 and portions of the first seal member 22. The mixing chamber 58 is spaced from the reaction chamber 56 and is surrounded by the second seal member 24 and other portions of the first seal member 22. However, due to the channels 26 and 28 formed between the ends of the second seal member 24 and the adjacent portions of the side walls of the first seal member 22, fluid disposed in either of the mixing chamber 58 or the reaction chamber 56 may flow easily therebetween. Col. 7, lines 3-24. Accordingly, the first and second seal member 22, 24 provide the vertical spacing for the reaction chamber 56 between the plate 12 and slide 50, as best shown in Figure 6.

The arrangement disclosed in McGrath does not teach or suggest the claimed separator which separates, i.e. forces apart, a sandwich of a substrate and cover slide. As described in the application, the sandwich includes a backing, a support substrate, and an interposed sealing gasket. Page 27, lines 6-8. Accordingly, the sandwich may include objects spaced relative to one another, e.g. by a gasket, or seals as described in McGrath. As described in the application, the separator separates, i.e. forces apart, portions of the substrate sandwich to "expose the . . . surface of the substrate to the desired processing reagents." Page 27, lines 17-22. In contrast to any spacing inherent to the sandwich itself, the claimed separators separate the portions of the sandwich, e.g. to expose the inner surface to the desired processing reagents. This is neither taught nor suggested by the cited art, particularly McGrath.

Further, modifying the probe of McGrath to include a wedge or other structure, as proposed by the Examiner, to provide spacing within the sandwich does not provide the claimed invention, which includes separator structure that separates one portion of the sandwich from another portion of the sandwich to expose an inner portion of the sandwich to fluid within the housing chamber.

Further still, modifying the probe of McGrath to include a separator that acts to separate, or force apart, or part, a sandwich of a substrate and a cover slide, and thus provide exposure to any fluid/reagent within the housing chamber (see application, page 27, lines 19-24), would change the principle of operation of the McGrath device, which provides for seal members that create separate mixing and reaction chambers within a

common seal. The fluid reagent, such as a blocking agent, is added to the tissue section within the common seal. Thus, McGrath provides that the chambers remain sealed during exposure of the tissue samples to the reagent. See col. 3, line 39 – col. 4, line 8. Accordingly, reconsideration and withdrawal of the rejection of claim 12 are requested respectfully.

Exposure to the desired processing reagents/fluids is expressly recited in new claim 48. This is neither taught nor suggested by McGrath. New claim 51 is similarly patentable. Allowance of new claims 48 and 51 are requested respectfully.

Claim 13 depends from claim 12 and is likewise patentable. In addition, claim 13 recites that the separator comprises a pair of flexible members having a wedge member therebetween. This structure is neither taught nor suggested by the cited art.

For at least these reasons, reconsideration and withdrawal of the rejections of claims 11-15, and 37-44, and allowance of new claims 48 and 51 are requested respectfully.

**Claims 45, 46, 49, 50, 52 and 53**

Claim 45 is believed allowable for reasons similar to those set forth above for claims 12, 13 and 45. In particular, as amended herein, claim 45 recites a flow device comprising "a separator mechanism for separating said substrate surface from said cover slide while in said reaction chamber without damage to said biopolymers on said surface." As discussed above, separating as used herein relates to the act of

separating the substrate surface from the cover slide, as is clear from the amended claim language, and from the specification read as a whole. This is recited in greater detail in claim 46, which requires that the separator mechanism comprise a pair of flexible members having a wedge member therebetween and disposed to insert between and separate said substrate surface from said cover slide. New claim 49 recites that the separator is configured to separate said substrate from said cover slide to expose said plurality of biopolymers to fluid within said housing chamber. New claim 50 recites that the wedge member is positioned to separate said substrate from said cover slide to expose said plurality of biopolymers to fluid within said housing chamber. New claims 52 and 53 are similar to claims 49 and 50 but recite that the separator is configured to "part" said substrate from said cover slide, in emphasis of certain distinctions over McGrath.

This is neither taught nor suggested by the cited art, particularly McGrath, and clearly distinguishes over the probe in McGrath which merely includes a "sandwich" having internal spacing.

For at least these reasons, reconsideration and withdrawal of the rejections of claims 45 and 46, and allowance of new claims 49, 50, 52 and 53 are requested respectfully.

**CONCLUSION**

In view of the foregoing amendments and remarks, Applicant believes claims 1-18 and 29-55 to be patentable and the application in condition for allowance, and request respectfully issuance of a Notice of Allowance. If any issues remain, the undersigned requests a telephone interview prior to the issuance of an action.

Respectfully submitted,

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